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Naltrexone and Amperozide Modify Chocolate and Saccharin Drinking in High Alcohol-Preferring P Rats

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BIGGS, T. A. G. AND R. D. MYERS. *Naltrexone and amperozide modify chocolate and saccharin drinking in high alcohol-preferring P rats.* PHARMACOL BIOCHEM BEHAV **60**(2) 407–413, 1998.—Previous studies showed that the 5-HT_2 receptor antagonist, amperozide, is somewhat more potent than the opiate antagonist, naltrexone, in reducing alcohol drinking in high alcohol-preferring (P) rats. The purpose of this study was to determine in the P rat whether the effect of either drug could be due, in part, to an alteration in gustatory function. In an unlimited, 24-h free choice paradigm, P rats were offered water simultaneously with either a highly palatable 0.1% saccharin solution or a 1:4 dilution of Nestlé Sweet Success chocolate drink. Throughout all phases of the study, the P rats always consumed significantly greater volumes of the chocolate drink than of the saccharin solution, i.e., 526 ml/kg vs. 181 ml/kg, respectively. Successive 12-day experimental periods consisted of three phases: a 4-day predrug control interval; 4 days of administration of saline control vehicle or either drug; and a final 4 day postdrug interval. In a counterbalance design, saline, amperozide (1.0 or 5.0 mg/kg) or naltrexone (2.5 or 5.0 mg/kg) was administered subcutaneously twice daily at 1600 and 2200 h for 4 days. Amperozide and naltrexone significantly reduced the drinking of chocolate in a dose-dependent manner. Conversely, only the two higher doses of amperozide and naltrexone decreased the intake of saccharin significantly. Thus, these findings suggest that different populations of central serotonin and opioid receptors concurrently underpin, in part, the preferences for both palatable and/or nutrient fluids. Finally, because both the opiate and 5-HT_{2A} antagonists reduce the ingestion of saccharin and chocolate solutions differentially, it is apparent that preferences for alternative palatable fluids should be examined when candidate drugs are screened for suppressing alcohol drinking and ultimately the treatment of alcohol abuse. © 1998 Elsevier Science Inc.

Amperozide (FG5606) Naltrexone Alcohol drinking P rats Chocolate drink Saccharin
Serotonin receptors Opiate receptors Alcoholism Ethanol preference Drinking Rats

SEVERAL pharmacological approaches have been used to suppress drinking of alcohol in experimental animals in relation to the treatment of alcoholism. For example, the opiate receptor antagonists, naloxone and naltrexone, diminish transiently the abnormal drinking of alcohol under certain experimental conditions (9,26,31,33,35,39,46). Similarly, certain drugs that inhibit the functional properties of endogenous serotonin (5-HT) in the CNS, such as fluoxetine and sertraline, also reduce transiently the self-selection of alcohol (6,16,21,32,37,38, 45). Because these drugs may also cause adverse side effects including anorexia and adipsia, their therapeutic potential presently remains uncertain (11,35,37). Other agents that act as an agonist of the 5-HT_1A receptor, such as buspirone, also reduce transiently the self selection of alcohol (6,16,21,32, 37, 38,45) without necessarily altering feeding behavior or inducing other side effects. Further, the 5-HT_{2A} receptor antagonist, amperozide (50), which possesses both anxiolytic and antipsychotic properties (2,4), suppresses alcohol drinking in rats without side effects on food or water intakes or other functions (34). Amperozide exerts this action in rats induced to drink by pretreatment with cyanamide (41) as well as in the high alcohol-preferring (P) rat (36,42,48). When amperozide is delivered continuously by minipump over 7 days, alcohol drinking is irreversibly suppressed (43). In each case, amperozide given in doses that are efficacious in reducing alcohol drinking is without significant side effects on food intake. This finding represents a critical variable in view of the caloric value of alcohol (11,37).

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A major question in this field now concerns the specificity of action of both naltrexone and amperozide on alcohol drinking, in relation to their influence on gustatory and olfactory processes related to the reinforcing properties of the fluid. Conceivably, a conditioned taste aversion may underlie the mechanism of action of a drug such as pCPA or fluoxetine in the suppression of alcohol drinking. For example, the pairing of saccharin drinking with the administration of zimeldine, reduces the intake of this sweet solution momentarily, which resumes on cessation of the drug (18). The purpose of this study, therefore, was to determine the effect of two drugs, which attenuate alcohol preference, on the volitional drinking of two highly palatable solutions. In these experiments, the alcohol-preferring P rat was selected (25) because of its preference for concentrations of alcohol up to 20 to 25% over water, with a maximum intake often exceeding 10 g/kg per day (23, 24). Amperozide and naltrexone were administered twice daily to the animals while they were offered water simultaneously with a solution of either a highly palatable chocolate drink or saccharin. Each dose of the drugs was selected on the basis of that which significantly attenuates alcohol preference in a free-choice situation (24,36).

METHOD

Male P rats ($n = 14$), weighing from 600–725 g, were obtained from the Indiana University Alcohol Research Center (Indianapolis, IN). Each rat was housed individually in a wire mesh cage in a temperature-controlled room at 22–24°C and maintained on a 12 L:12 D cycle, with lights on at 0700 h. The rats were provided unlimited access to Agway NIH-07 formulation rat chow and tap water throughout the experiment. All experimental procedures used in this study were approved by the internal animal use committee of the School of Medicine and were in strict compliance with the guidelines of the National Institutes of Health for the care and use of laboratory animals.

Test Solutions

A solution of a chocolate flavored nutritional supplement (Nestlé Sweet Success Dark Chocolate Fudge Diet Drink) was made up in a 4:1 dilution (23). The caloric values of the chocolate solution and food pellets were 0.12 kcal/ml and 4.0 kcal/g, respectively. A solution of saccharin was prepared also in tap water in a concentration of 0.1% in general accord with previous reports (7,14,27,28,52). Special watering bottles with a capacity of 750 ml were filled with either the solution of chocolate or saccharin; these bottles were selected over the 100 ml kimax tubes because of the copious quantities of both the chocolate and saccharin solutions consumed by the P rats (23). A stainless steel bowl was placed beneath each cage for collection of either leaked fluid. Tap water was always available as the alternative fluid, and at 0830 h on each day, measures of food and fluid intakes as well as body weights were recorded.

Experimental Design

The P rats were divided into two equal groups for their respective patterns of drinking of the chocolate drink ($n = 7$) and saccharin solution ($n = 7$). During the first 4-day interval, comprising a predrug control period, each rat was offered ad lib water, food, and either the chocolate or saccharin solution. Over the next 4-day test interval, either the saline control vehicle, amperozide (1.0 or 5.0 mg/kg) or naltrexone (2.5 or 5.0 mg/kg) was injected subcutaneously twice daily at 1600 and 2200 h. Thus, the total daily doses of amperozide and naltrexone were 2.0 or 10.0 mg/kg and 5.0 or 10.0 mg/kg, respectively. The two doses of each drug were selected on the basis of previous findings on the efficacy of these drugs in attenuating alcohol preference in P, HAD, and cyanamide-treated rats (9, 24,36,41,42). The solution of each drug was prepared daily in the sterilized 0.9% saline control vehicle. After the injection series was completed, the rats were tested over a third and final 4-day period to determine whether an effect on chocolate or saccharin drinking of amperozide or naltrexone would persist. Each subgroup comprised of three and four rats was rotated according to a counterbalanced design so that every rat in each subgroup received each dose of the drug and the control saline vehicle.

Data Analysis

Each of the measures recorded daily, including kcals derived from food and the chocolate solution, were transcribed to the Microsoft Excel software program. All data were analyzed using the Instat software program. Analyses of variance were used to determine the differences between the intakes of the chocolate drink, saccharin solution, food, and water as well as measures of body weight during each of the 4-day test periods. A p-value of <0.05 was considered to be statistically significant.

RESULTS

Amperozide injected twice daily in doses of 1.0 mg/kg and 5.0 mg/kg attenuated the volitional consumption of both the chocolate flavored drink and the saccharin solution to different degrees. Similarly, the 2.5 mg/kg and 5.0 mg/kg doses of naltrexone also modified the intakes of saccharin and chocolate solutions.

Drug Effects on Chocolate Intake

An analysis of the mean intake over 4 days of the chocolate drink following injections of amperozide, naltrexone, and saline is presented in Fig. 1. Amperozide reduced the ml/kg per day ingestion of the chocolate solution significantly during administration of 1.0 and 5.0 mg/kg from the mean predrug control intake of 450 ± 14 to 372 ± 28 ml/kg per day, $F(1, 47) = 5.0$, $p < 0.05$, and to 244 ± 29 ml/kg per day, $F(1, 47) = 33.0$, $p < 0.01$, respectively. During the 4-day postinjection period, the intakes of chocolate returned differentially to over 350 ml/day. The low and high doses of naltrexone also reduced the drinking of the chocolate drink from 450 ± 14 to 398 ± 38 (NS) ml/kg per day and to 359 ± 28 ml/kg per day, $F(1, 47) = 6.6$, $p < 0.05$, respectively (Fig. 1). During the postdrug interval, chocolate intake was still suppressed after 2.5 mg/kg naltrexone $F(1, 47) = 5.9$, $p < 0.05$. In addition, the chocolate intakes of both naltrexone- and amperozide-treated groups were all significantly lower than that of the saline control ($p < 0.01$).

As presented in Fig. 2, the high dose of amperozide reduced the food intake of the P rats having unlimited access to the chocolate solution. The mean daily intakes of food during the administration of the 5.0 mg/kg dose of the 5-HT_2A antagonist declined from 19.7 ± 0.6 to 12.1 ± 1.2 g/day, $F(1, 47) = 24.2$, $p < 0.01$, but rebounded significantly during the postdrug interval to 23.0 ± 0.8, $F(1, 47) = 9.4$, $p < 0.01$. Although the higher dose of naltrexone also diminished the food consumed during the first 2 days (Fig. 2), the overall decline was not significant.

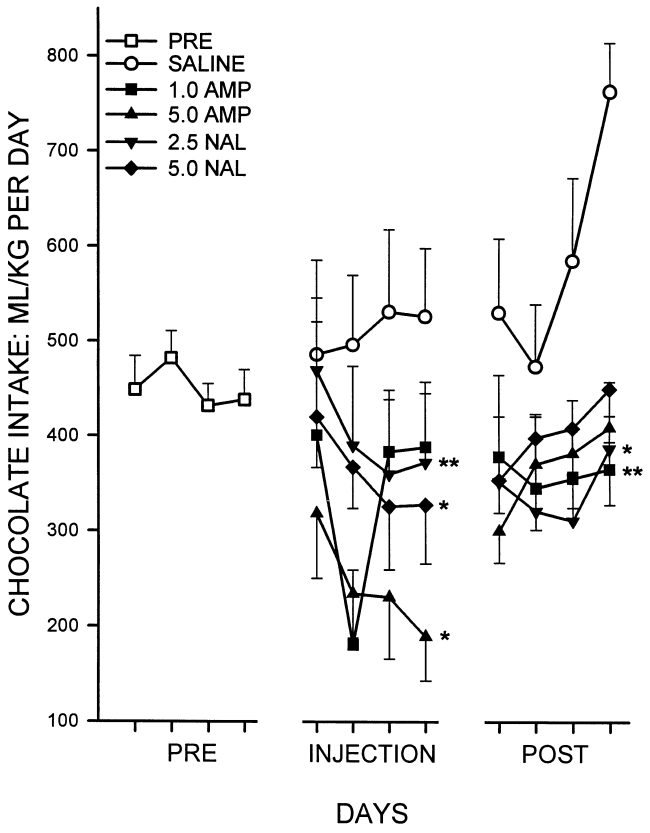

FIG. 1. Mean ± SE intakes of the chocolate solution by P rats in ml/kg per day over: 4 days before injection (PRE): 4 days during injection b.i.d. (INJ) of the saline control vehicle or of 1.0 or 5.0 mg/kg amperozide (AMP) and 2.5 or 5.0 mg/kg naltrexone (NAL); and 4 days after injections ended (POST). $n = 7$ per drug group; $n = 6$ in saline group.

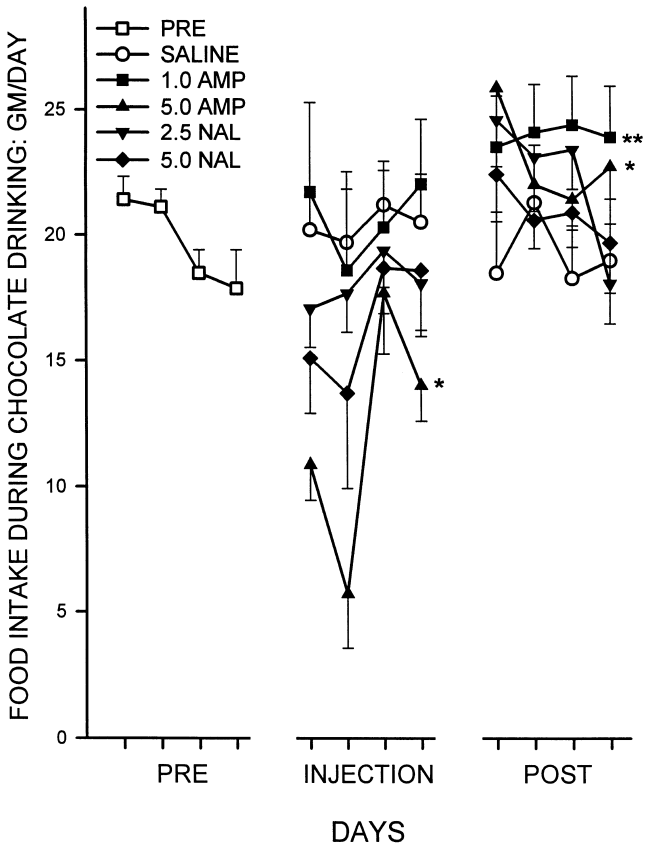

FIG. 2. Mean ± SE intakes of food in g/day in P rats during drinking of the chocolate solution over: 4 days before injection (PRE): 4 days during injection b.i.d. (INJ) of the saline control vehicle, or of 1.0 or 5.0 mg/kg amperozide (AMP) and 2.5 or 5.0 mg/kg naltrexone (NAL); and 4 days after injections ended (POST). $n = 7$ per drug group; $n = 6$ in saline group.

Proportion of kcal Obtained From Chocolate

The amount of kcal derived from the chocolate solution during the interval of administration of either amperozide or naltrexone is illustrated in Fig. 3. During injections of either amperozide or naltrexone, the mean daily proportion over 4 days of kcal obtained from the chocolate drink failed to change significantly. However, during the postdrug period, the 5.0 mg/kg of amperozide reduced kcal intake from 0.31 ± 0.02 to 0.23 ± 0.02, $F(1, 47) = 7.6$, $p < 0.01$; moreover, naltrexone at the low and high doses suppressed kcal ingested from 0.31 ± 0.02 to 0.23 ± 0.02, $F(1, 47) = 7.6$, $p < 0.01$, and to 0.25 ± 0.02 $F(1, 47) = 4.3$, $p < 0.05$.

Drug Effects on Saccharin Intake

As shown in Fig. 4, both the 1.0 mg/kg and 5.0 mg/kg doses of amperozide lowered the mean intake over 4 days of saccharin significantly from 161 ± 11 to 108 ± 11 ml/kg per day, $F(1, 47) = 10.7$, $p < 0.01$, and to 45 ± 4, $F(1, 47) = 123.8$, $p < 0.01$, respectively. Although the attenuation of saccharin intake by the 2.5 mg/kg dose of naltrexone was not significant, the 5.0 mg/kg dose reduced saccharin drinking from 161 ± 11 to 83 ± 5 ml/kg per day, $F(1, 47) = 52.2$, $p < 0.01$. During the 4-day postinjection period, the intakes of saccharin remained suppressed by the low and high doses of naltrexone at 105 ± 9 ml/kg per day, $F(1, 47) = 14.5$, $p < 0.01$, and 99 ± 7 ml/kg per day, $F(1, 47) = 23.6$, $p < 0.01$.

As the rats drank the saccharin solution, the mean daily intakes of food over 4 days decreased significantly (Fig. 5) during injections of both 1.0 mg/kg and 5.0 mg/kg doses of amperozide from 30 ± 0.3 to 25 ± 1 g/day, $F(1, 47) = 21.0$, $p < 0.01$, and to 19 ± 1 g/day $F(1, 47) = 65.5$, $p < 0.01$, respectively. Further, naltrexone in both low and high doses also significantly reduced the feeding response of the rats from 30 ± 0.3 to 27 ± 0.6 g/day, $F(1, 47) = 13.3$, $p < 0.01$ and to 26 ± 0.6 g/day, $F(1, 47) = 13.9$, $p < 0.01$, respectively.

The body weights as well as intakes of water of the rats consuming chocolate and saccharin solutions are presented in Table 1. Amperozide reduced mean body weight during injection only of the 5.0 mg/kg dose during chocolate drinking from 642 ± 11.2 to 613 ± 11.5 g, $F(1, 55) = 6.9$, $p < 0.05$. During the interval of saccharin drinking amperozide lowered body weight from 717 ± 8 to 691 ± 8 g, $F(1, 55) = 6.6$, $p < 0.05$, which persisted postdrug to 697 ± 6 g, $F(1, 55) = 5.3$, $p < 0.05$. As shown in Table 1, water intakes increased significantly during administration of 5.0 mg/kg amperozide and 2.5 mg/kg naltrexone.

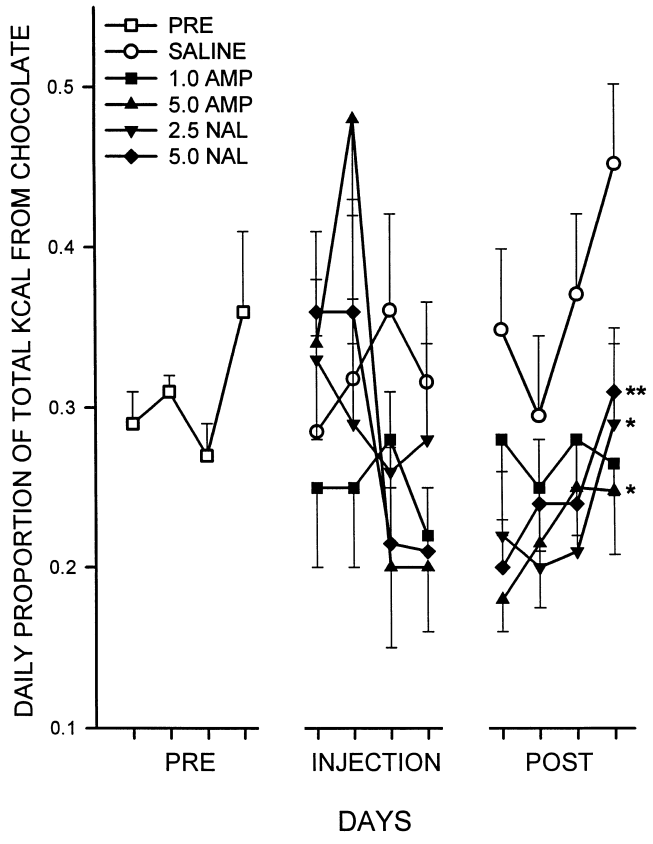

FIG. 3. Mean ± SE proportion of total Kcal derived from chocolate consumed daily in P rats over: 4 days before injection (PRE): 4 days during injection b.i.d. (INJ) of the saline control vehicle, or of 1.0 or 5.0 mg/kg amperozide (AMP) and 2.5 or 5.0 mg/kg naltrexone (NAL); and 4 days after injections ended (POST). n = 7 per drug group; n = 6 in saline group.

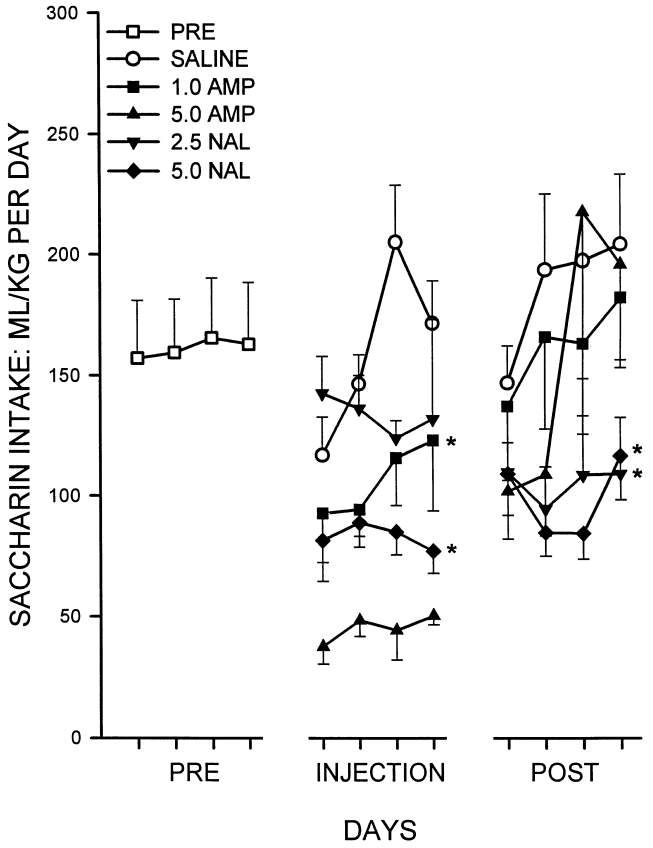

FIG 4. Mean ± SE intakes of the saccharin solution by P rats in ml/kg per day over: 4 days before injection (PRE): 4 days during injection b.i.d. (INJ) of the saline control vehicle, or of 1.0 or 5.0 mg/kg amperozide (AMP) and 2.5 or 5.0 mg/kg naltrexone (NAL); and 4 days after injections ended (POST). n = 7 per drug group; n = 6 in saline group.

DISCUSSION

In previous studies, the central mechanisms of action of amperozide and naltrexone were compared in terms of their attenuation of alcohol preference in drinking rats (24,36). Whereas both drugs reduced the intake of alcohol, the 5-HT_2A receptor antagonist was somewhat more potent (36), and the decline in intake persisted over a 4-day injection sequence. In contrast to the relatively transient action of amperozide on chocolate drinking, this 5-HT_{2A} antagonist exerts a prolonged effect in suppressing alcohol preference after its administration is discontinued (41,43). Moreover, amperozide produces a somewhat greater percent reduction in the intake of alcohol in the genetic drinking rat compared to chocolate or saccharin solutions, which suggests separate mechanisms underlying the reinforcing property of different fluids (36,41,42). In this connection, olfactory factors are also involved in drinking of the P rat in that the activity of the animal intensifies when it is exposed to the odor of its preferred alcohol concentration (40). Taken together, therefore, central 5-HT_{2A} receptors presumably underlie general central mechanisms responsible for a broad spectrum of palatable, reinforcing substances.

The present results demonstrate striking similarities in the effects of the pharmacological antagonist of 5-HT_{2A} and opiate receptors on the drinking of highly palatable solutions of saccharin and a nutritious chocolate drink in the alcohol-preferring P rat. Amperozide caused a dose-dependent suppression of the preference of both palatable solutions as well as a reduction in the intake of food in the presence of either chocolate or saccharin. Although a high dose of amperozide can suppress feeding, as reported previously (2,4,42), doses below 5.0 mg/kg per day generally exert little effect on ingestive behavior or body weight either during or following its administration (41,42). However, in these experiments, amperozide caused a transient decline in the ingestion of food concomitant with chocolate drinking; this finding corresponds to that of other drugs such as fluoxetine, zimelidine, and sertraline, which inhibit 5-HT uptake and diminish the intakes of both food and alcohol concurrently (6,11,16,37). Consequently, amperozide in high doses may impair the central regulation of caloric intake, which would suggest that the antagonism of 5-HT_2A receptors can affect both central ingestive and reinforcing processes in a nonspecific manner.

In terms of its mechanism of action, amperozide enhances extracellular levels of 5-HT in the brain of the rat by inhibiting its uptake (10). Such an elevation of 5-HT by the antagonism of 5-HT_{2A} receptors, now implicated in the drinking of alcohol or other preferred fluid (49), may explain the action of amperozide in decreasing the ingestion of the chocolate

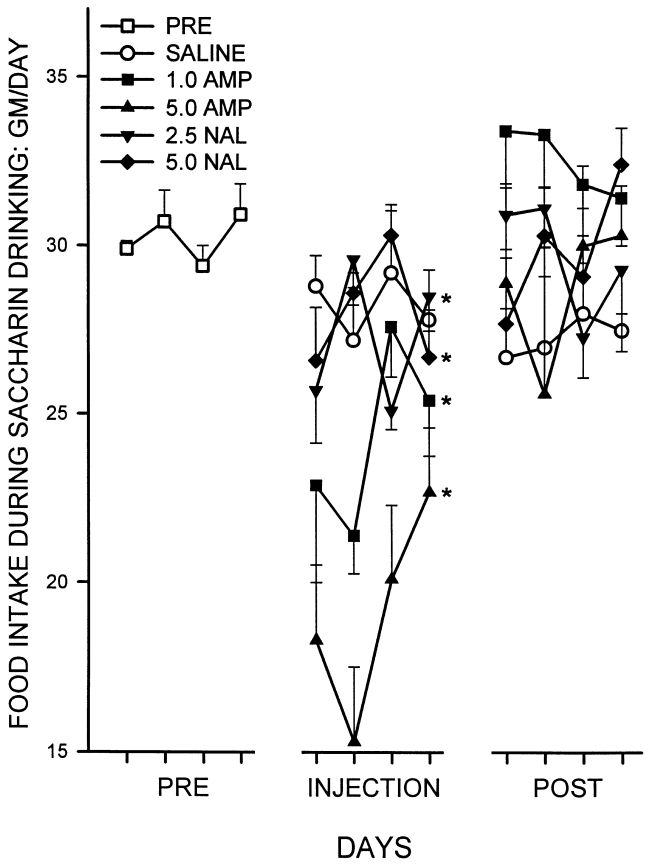

FIG. 5. Mean ± SE intakes of food in g/day in P rats during drinking of the saccharin solution over: 4 days before injection (PRE): 4 days during injection b.i.d. (INJ) of the saline control vehicle, or of 1.0 or 5.0 mg/kg amperozide (AMP) and 2.5 or 5.0 mg/kg naltrexone (NAL); and 4 days after injections ended (POST). $n = 7$ per drug group; $n = 6$ in saline group.

drink. Because amperozide also releases dopamine preferentially from neurons in the mesolimbic reward system (10,15, 20), an upregulation of dopamine receptors in this pathway could impair normal dopaminergic function to attenuate the reinforcing qualities of both chocolate and saccharin. Thus, select populations of 5-HT and opioid receptors not only are likely involved in the selection of a fluid (23,33) but dopamine receptors apparently play an equal role in the preference for a palatable or nutritious fluid in genetic lines of rat (30,33).

The antagonism of opiate receptors by naltrexone significantly alters the gustatory component of the rat's fluid intake by decreasing both the sweet nonnutrient solution as well as that of the highly palatable and nutrient chocolate drink. Thus, the systemic administration of naloxone or naltrexone apparently disrupts the overall functional regulation of ingestive behavior in the rat. These opiate receptor antagonists can suppress the intake of water even in 24- to 48-h fluid-deprived rats (44) as well as liquid or solid sucrose in the vagotomized rat (5). Moreover, naloxone and naltrexone attenuate drinking of nonnutrient saccharin under a variety of experimental conditions in rats and mice (7,28,52). Further, when naltrexone is delivered chronically by osmotic minipump to the rat, its metabolic rate and food intake are also depressed and hypothermia is induced (29). In relation to our results, naltrexone suppresses the intake of highly palatable chocolate cookies, which leads to a compensatory rise in eating of ordinary chow (8). When palatable and ordinary foods are presented concurrently to the rat, naloxone reduces the hyperphagic response of rats for a preferred diet but not the nonpreferred diet (12,13); however, in the sated human subject, naltrexone fails to interfere with feeding or the feelings of hunger or satiety (17). In the present experiment, the saccharin solution was continuously available, which eliminated any confounding influence of hunger due to food deprivation. In fact, when a measure of feeding is taken during saccharin drinking more than 1 h after it is presented, the cumulative intake of food is unaffected (14).

TABLE 1

MEAN ± SEM OF BODY WEIGHT (g) AND WATER INTAKE (ml) OF ALL TREATMENT GROUPS DURING A 4-DAY PREDRUG PERIOD, 4 DAYS OF DRUG OR CONTROL INJECTIONS (Inj), 4 DAYS AFER INJECTIONS (POST)

	Saline	Amperozide 1.0 mg/kg	Amperozide 5.0 mg/kg	Naltrexone 2.5 mg/kg	Naltrexone 5.0 mg/kg
	BODY WEIGHT OF RATS DURING CHOCOLATE DRINKING				
Pre	603 ± 8.2	676 ± 5.6	642 ± 11.2	635 ± 12.0	636 ± 10.9
Inj	603 ± 8.0	664 ± 5.8	613 ± 11.5	636 ± 11.7	638 ± 10.5
Post	610 ± 8.2	675 ± 4.7	629 ± 11.0	638 ± 11.3	643 ± 10.9
	BODY WEIGHT OF RATS DURING SACCHARIN DRINKING				
Pre	656 ± 13.5	687 ± 5.6	717 ± 7.7	709 ± 6.7	706 ± 6.8
Inj	658 ± 14.2	676 ± 6.7	691 ± 7.6*	714 ± 6.6	707 ± 7.4
Post	661 ± 13.5	689 ± 6.8	697 ± 6.3*	721 ± 7.0	713 ± 9.0
	WATER INTAKE OF RATS DURING CHOCOLATE DRINKING				
Pre	1.3 ± 0.3	3.1 ± 1.0	3.0 ± 1.2	1.8 ± 0.6	1.1 ± 0.3
Inj	1.7 ± 0.6	2.3 ± 0.4	2.5 ± 0.5	2.0 ± 0.3	1.5 ± 0.3
Post	1.3 ± 0.4	1.8 ± 0.5	1.8 ± 0.9	4.4 ± 1.8	0.9 ± 0.1
	WATER INTAKE OF RATS DURING SACCHARIN DRINKING				
Pre	1.7 ± 0.3	1.2 ± 0.2	2.0 ± 0.4	1.1 ± 0.2	1.1 ± 0.2
Inj	2.0 ± 0.4	1.5 ± 0.2	6.1 ± 1.2*	2.3 ± 0.4*	2.0 ± 0.5
Post	1.2 ± 0.2	1.8 ± 1.0	4.2 ± 1.3	1.6 ± 0.3	1.8 ± 0.4

N = 7 per drug group; N = 6 in saline group.
*$p < 0.05$.

The central infusion of naloxone by the intracerebroventricular (ICV) route diminishes saccharin drinking almost immediately (1,14). Further, a delta or kappa receptor antagonist infused ICV also reduces the consumption of a combined saccharin–sucrose solution or saccharin alone (1,3), which implies that different opiate receptor subtypes underlie the preference for both sweetened and calorie rich solutions. This fact is substantiated by the finding that naloxone causes a concurrent reduction of both palatable sucrose and alcohol solutions (47). Further, the delta receptor antagonists, ICI 17864 and naltrindole, reduce drinking not only of a preferred alcohol solution in the P rat, but also saccharin intake, which again supports the important role of delta receptors in gustatory functions (22). Recently, it was shown that opioid antagonists can interact with 5-HT drugs in that a 5-HT_3 antagonist (ICS 205930) influences the reduced sucrose intake produced by naltrexone (19). Moreover, the 5-HT_3 antagonist, ondansetron, suppresses the ingestion of food dose dependently in the ad lib food situation (51).

A general conclusion that can be deduced from the present results is that a candidate drug considered for the potential treatment of alcohol abuse should be tested in animals offered palatable or nutrient solutions simultaneously with alcohol in a free-choice situation (34). Thus, if a drug alters the preference for alcohol and a palatable solution indiscriminately, its mechanism of action apparently is nonselective in terms of taste, pleasing odor, caloric value, or central reinforcement processes. However, if the test drug modifies the preference for alcohol specifically in the presence of a palatable solution, its specificity of action on craving or the addictive component of alcohol would be confirmed.

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